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Interpersonal sensitivity and persistent attenuated psychotic symptoms in adolescence

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Abstract

Background: Interpersonal sensitivity defines feelings of inner-fragility in the presence of others due to the expectation of criticism or rejection. Interpersonal sensitivity was found to be related to attenuated positive psychotic symptom during the prodromal phase of psychosis. The aims of this study were to examine if high level of interpersonal sensitivity at baseline are associated with the persistence of attenuated positive psychotic symptoms and general psychopathology at 18-months follow-up.

Methods: A sample of 85 help-seeking individuals (mean age=16.6, SD=5.05) referred an Italian early detection project, completed the Interpersonal Sensitivity Measure (IPSM) and the Structured Interview for Prodromal Symptoms (SIPS) at baseline and were assessed a 18-months follow-up using the SIPS.

Results: Results showed that individuals with high level of interpersonal sensitivity at baseline reported high level of attenuated positive psychotic symptoms (i.e. unusual thought content) and general symptoms (i.e. depression, irritability and low tolerance to daily stress) at follow-up.

Conclusions: This study suggests that being “hypersensitive” to interpersonal interactions is a psychological feature associated with attenuated positive psychotic symptoms and general symptoms, such as depression and irritability, at 18-months follow-up. Assessing and treating inner-self fragilities may be an important step of early detection program to avoid the persistence of subtle but very distressing long-terms symptoms.

Key words: interpersonal sensitivity; ultra high risk; negative affective states; psychosis; adolescents.

Introduction

Given the common occurrence of nonpsychotic disorders in ultra-high-risk (UHR) population (1-5) and the declining rate of transition to psychotic disorder in recent cohorts (6-11), authors have examined the outcomes of the individuals who do not develop psychosis (12-14). Results showed that the majority of those who do not develop psychosis are still at significant risk for continued attenuated psychotic symptoms and many experience mood disorder, anxiety disorder and substance use disorder (12, 13, 15). At baseline, the different clinical presentations are indistinguishable (16). Thus, baseline high-risk psychopathology may reflect the emergence of underlying core prodromal features for psychotic disorders, may be associated with other nonpsychotic clinical conditions such as depression, or may be normal psychopathological variations in the general population that spontaneously remit (17, 18). This has led a number of researchers to suggest that the UHR intervention should focus on continuing psychopathology and treatment needs, regardless of transition status (19, 20).

To contribute to on-going research regarding outcome and risk factors of people with subtle psychotic symptoms who do not develop psychosis but still need clinical attention, the main aim of this study was to examine the relationship between baseline psychopathological characteristics and the persistence of longitudinal psychopathological features, such as attenuated positive psychotic symptom and general symptoms (i.e. depression, irritability and low tolerance to daily stress) at 18-months follow-up. In particular, the attention was focussed on a subjective psychopathological trait called interpersonal sensitivity that defines feelings of inner-self fragility in the presence of others due to the expectation of criticism or rejection (21). Individuals with this trait are preoccupied with interpersonal relationships, vigilant to the behaviour and mood of others, sensitive to perceived or actual criticism or rejection, and modified their behaviour to comply with others' expectations (21). Originally conceptualized as a set of symptoms occurring both as a consequence of depression and as a vulnerability for the development of depression (22, 23), interpersonal sensitivity was also found to be related to attenuated positive psychotic symptom during the prodromal phase of psychosis (24-27) and to paranoid ideation in general populations samples, UHR and individuals with psychosis (28-32). A previous cross-sectional research conducted among the baseline sample involved in the present study (27), found that UHR individuals showed high sensitivity to interpersonal interaction, high vigilance to others' behaviour in an attempt to gauge their response, as well as high level of anxiety about separation from significant others. On the

basis of the latter (27) and other previous studies (24-26; 28-32), confirming the correlation between interpersonal sensitivity and attenuated psychotic symptoms, and according to the role of interpersonal sensitivity as one of the vulnerability factors to depression (22, 23), we hypothesised that baseline level of interpersonal sensitivity would predict the longitudinal persistence of attenuated positive psychotic symptoms and general symptoms.

Methods

The sample consisted of 85 adolescents and young adults involved in the follow-up assessment of the early detection project “Liberiamo Il Futuro” (LIF). Full details of the study are provided in Brandizzi et al. 2014 (33). Briefly, LIF is a multicentre project carried out by the contribution of Sapienza University of Rome and six Adult Mental Health Service (AMHS) and six Child and Adolescents Mental Health Services (CAMHS) located in one of the eight Local Health Districts of Rome, Italy, i.e. the Rome H area; its main aim is to identify individuals at high-risk for developing a psychosis according to the at risk mental state for psychosis (UHR) and the Basic Symptoms (BS) criteria among help-seeking adolescents (age range: 12–18 years) and young adults (18–35 years).

The inclusion criteria were: age between 12 and 35 years; IQ ≥ 70; sufficient knowledge of the Italian language; the disorder is not secondary to or correlated with a general medical condition; willingness and ability to provide free written informed consent (the informed consent was provided by parents or guardian in case of minor). Source of referrals were GPs and other health care specialists, family members and friends, school members and legal agencies as well as self-referrals.

The total baseline sample of LIF consisted of 367 adolescents and young adults help-seekers for psychological problems. Based on a combination of Prodromal Questionnaire (PQ-92; 34) positive symptoms scale scores (cut-off of 18) and clinical impression (a semi-structured interview named Clinical Impression Assessment of the Pre-psychotic Phase of Schizophrenia – CIAPPS – was developed by our research group, to evaluate the first impression of clinicians facing a young subject independently from attenuated psychotic symptoms; its validation is under review) 188 participants were assessed with the Structured Interview for Prodromal Syndromes (SIPS; 35, 36) at baseline.

The whole assessment lasted approximately two and half hour and it was usually conducted over two sessions. Assessments were conducted by the same psychiatrist, resident in psychiatry or a clinical psychologist trained in administering the SIPS.

After eighteen months from the initial referral, regardless the presence of At Risk Syndrome for Psychosis according to SIPS, 103 of participants accepted to be evaluated again. Of these, 85 had completed the baseline assessment of interpersonal sensitivity and were therefore involved in the present study.

Measures

Socio-demographic (age, gender, educational level, employment status) as well as referral reason, and details about previous psychiatric treatment, psychiatric diagnosis and psychiatric treatment between baseline and follow up were recorded during a clinical assessment using a semi-structured interview.

Interpersonal Sensitivity Measure (IPSM)

To measure interpersonal sensitivity, we used the Italian version (37) of Interpersonal Sensitivity Measure (IPSM; 21) a 36-item self-report questionnaire. Self-statements are rated on a four-point scale (1=very unlike self, 4=very like self). The level of interpersonal sensitivity is calculated by summing up the scores for each item. The factor structure of the IPSM consists of the following five components: (1) “interpersonal awareness” (seven items, range 1–28); (2) “need for approval” (eight items, range 8–32); (3) “separation anxiety” (eight items, range 8–32); (4) “timidity” (eight items, range 8–32); and (5) “fragile inner-self” (five items, range 5–20). The IPSM has been found to have good internal consistency (a values from 0.85 to 0.86), test–retest re- liability (r=0.70) and correlation with clinical judgment ratings of interpersonal sensitivity (r=0.72) (21).

Structured Interview for Psychosis-risk Syndromes (SIPS)

The SIPS (35, 36) is a clinician-administered, semi-structured interview specifically designed to establish the risk of psychosis. The Scale Of Prodromal Symptoms (SOPS), the rating scale of the SIPS, has four 4 SIPS subscales that include five Positive Symptom items, six Negative Symptom items, four Disorganization Symptoms items and four General Symptom items. All symptoms are rated on a 7-point rating scale rating from 0 (Never, absent) to 6 (Severe/Extreme and Psychotic for the positive items).

Structured Clinical Interview (SCID-I) for DSM-IV and Kiddie-Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-SADS-PL)

Axis I diagnoses were evaluated with the SCID-I (age 19–35; 38) and with the K-SADS-PL (age 12–18 years; 39).

Data analysis

Statistical analyses were performed using SPSS version 20 (SPSS Inc., USA). Descriptive statistics including mean and standard deviation values for continuous variables and frequencies for categorical variables were calculated. Mann-Whitney U test and Kruskal-Wallis test were used for correlation between categorical values at baseline and at follow-up and interpersonal sensitive subscales at baseline. Results were corrected for Bonferroni's multiple comparisons. Pearson's correlation was calculated for continuous variables at baseline and at follow-up and interpersonal sensitive subscales at baseline. Association between baseline interpersonal sensitivity and follow-up attenuated positive psychotic symptoms were explored by a linear regression-backward elimination. Attenuated positive psychotic symptoms were involved as the dependent variable, interpersonal sensitivity (total and each subscales' scores) as the predictor. Linear regression-backward elimination was also used to evaluate the relationship between baseline interpersonal sensitivity and other psychopathological follow-up features, such as general symptoms (i.e. depression, irritability and low tolerance to daily stressful events). The level of statistical difference was set at $p<0.05$ and all reported significance values were two- tailed.

Results

A summary of the participant socio-demographic characteristics at baseline is provided in Table 1.

Table 1 around here

Eighty-five subjects were involved in the present study. The mean age of the sample at baseline was 16.36 (SD 5.05) years. About 50% of the follow-up participants were male (52.9%; N=45). The main reason for referral was anxiety (24.7%; N=21), followed by school problems (23.5%; N=20) and depression/mood liability (20.0%; N=17). After the full

assessment at baseline, the majority of the sample resulted affected by an anxiety disorder (N=29, 34.1%) followed by mood disorders (N=27; 31.8%).

The socio-demographic and psychopathological features of the sample after 18 months from the first contact with mental health services are summarized in Table 2.

Table 2 around here

Forty-eight participants (57.1%) received treatment between baseline and follow-up assessment: 37 (44%) psychotherapeutic treatment and 26 (31%) pharmacological treatment; only three (3.6%) participants needed in-patient treatment.
IPSM scores in our sample were lower than those found in other UHR and depressive samples (21, 26-28) but higher than those found in healthy controls (21, 32).

Fifty-five participants (65.6%) did not meet criteria for UHR (N-UHR) according with SIPS at baseline. The majority of N-UHR participants (N=56, 65.9%) did not develop a UHR state at follow-up. Of those who met UHR at baseline, four (4.7%) participants converted to full-blown psychosis. Interestingly, in the whole sample, the mean of the SIPS positive subscale score was high both at baseline (SIPS positive: 4.8, SD 4.24) and at follow up (SIPS positive: 5.19, SD 5.33); the higher rate of SIPS positive scores among UHR group (SIPS positive: 9.37, SD 3.52) as compared to N-UHR group (SIPS positive: 3.54, SD 5.02) may explain this result.

As shown in Table 1, interpersonal awareness ($p \leq 0.05$), separation anxiety ($p \leq 0.005$) and fragile inner-self ($p \leq 0.05$) IPSM subscale significantly correlate with SIPS general subscale at baseline, while fragile inner-self subscale ($p \leq 0.005$) also significantly correlate with SIPS positive subscale. As shown in Table 2, only interpersonal awareness ($p \leq 0.005$) and separation anxiety ($p \leq 0.05$) continued to significantly correlate with SIPS general subscale at 18-months follow-up, while fragile inner-self showed a significant correlation with SIPS positive subscale ($p \leq 0.05$).
A multiple regression was conducted to evaluate if interpersonal sensitivity dimensions (separation anxiety, timidity, interpersonal awareness, fragile inner-self, need for approval) was associated the total score of attenuated positive symptoms at follow-up measured by SIPS (see Table 3).

Table 3 around here

Using the backward method it was found that baseline need for approval and fragile inner-self subscale's scores explain 11% of the variance in the level of attenuated positive symptoms at follow-up (F (1, 81) =2.753, p = 0.007, R^2 =0.115, R^2 Adjusted =0.093). The analysis showed that fragile inner-self was significantly associated with higher levels of attenuated positive symptoms at follow-up (Beta = .306, t (2, 82) = 2.89, p=0.005). Need for approval inversely influenced the level of attenuated positive symptoms at follow-up (Beta = -.214, t (2, 82) = -2.01, p=0.047).

An analysis of standard residuals was carried out, which showed that the data contained no outliers (Std. Residual Min = -1.5, Std. Residual Max = 3.0). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (Tolerance = .96, VIF = 1.04). The data met the assumption of independent errors (Durbin-Watson value = 1.47). The histogram of standardised residuals indicated that the data contained approximately normally distributed errors, as did the normal P-P plot of standardised residuals, which showed points that were not completely on the line, but close.

The same procedure was conducted to investigate if interpersonal sensitivity dimensions (separation anxiety, timidity, interpersonal awareness, fragile inner-self, need for approval) level was related the total score of general SIPS symptoms at follow-up measured by SIPS (see Table 4).

Table 4 around here

Using the backward method it was found that baseline need for approval and interpersonal awareness subscale's scores explain 16.3% of the variance in the level of general SIPS symptoms at follow-up (F (2, 81) =7.95, p = 0.001, R^2=0.163; adjusted R^2= 0.142.). The analysis shows that level of baseline interpersonal awareness is significantly related levels of general symptoms at follow-up (Beta = .431, t (2, 82) = 3.87, p=0.000), while need for approval level is significantly inversely related value of general symptoms at follow-up (Beta =-0.276, t (2, 82) = -2.48, p=0.015).

Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (Tolerance = .96, VIF = 1.04). The data met the assumption of independent errors (Durbin-Watson value = 1.47). The histogram of standardised residuals

indicated that the data contained approximately normally distributed errors, as did the normal P-P plot of standardised residuals, which showed points that were not completely on the line, but close.

Discussion

This study explored the relationship between interpersonal sensitivity and clinical outcome for a sub-group of help-seeking young individuals involved in an Italian early detection project (LIF project). In line with our research hypothesis, we found that the sense of having an inner or core self that is unlikeable and needs to be hidden from others was associated to the presence of attenuated positive psychotic symptoms at follow-up. These findings confirm the results of previous studies conducted among UHR individuals (26-28).

In line with cognitive models of positive symptoms of psychosis, negative beliefs about the self as fragile and vulnerable to threat may lead to a tendency to attribute experiences as externally caused and in turn facilitate the persistence of paranoid ideation (31). Our results also showed that feelings of having a fragile and bothersome inner-self, with consequent social evaluative concerns (fears of rejections, feelings of vulnerability, thoughts that the world is potentially dangerous), may lead to the formation and maintenance of other attenuated positive psychotic symptoms, such as preoccupations with unusual valued ideas (religion and existential themes), magical thinking, notions of being unusually special or perceptual abnormalities. As the German psychiatrist E. Kretschmer described in 1925 (40), thoughts and fears of vulnerability, typical of sensitive individuals, may be related to concerns of dissimilarity and existential doubts; in some cases unbearable feelings of difference may produce pre-delusional mood and thoughts. Thus, the persistence of attenuated positive psychotic symptoms showed by our sample could be interpreted as a sort of protection from self-disparagement indicated by interpersonal sensitivity.

Moreover, it is important to underline the possible affinity between the notion of “fragile inner-self” and the phenomenological model of self-disturbance, defined by some authors as a core clinical feature of schizophrenia spectrum disorders (41, 42) and reported in young subjects at high risk for psychosis (43, 44). In particular, some aspect of this model (such as a “sense of inner void”, “a sense of passivity in relation to the world and others”, “experiencing the physical presence and contact of others as threatening to one’s existence in some way” and “a tendency to excessively monitoring inner life, while at the same time interacting in the world”; 45) may have some similarities to fragile inner self

aspects of interpersonal sensitivity. According to this model, the fragile inner-self aspect of interpersonal sensitivity could be considered as a first and less severe step of the psychotic breaking up; this similarity may, at least in part, explain the persistence in our sample of attenuated positive psychotic symptoms in subjects with core-self fragilities.

Our results also showed that a high score on "need for approval" was associated with more severe attenuated positive symptoms at follow-up. Being highly vigilant to others' behaviour could be an attempt to gauge their response and may reflect a tendency to search for interpersonal relationships, even if with insecurity; relating to others' thoughts and emotions may help to avoid the development of pre-delusional ideas and other attenuated positive psychotic symptoms.

Previous studies found that interpersonal sensitivity was closely linked to low self-confidence, feelings of insecurity and low self-esteem (21). For this reason it was first conceptualized as a psychopathological aspect occurring both as a consequence of depression and as a vulnerability for the development of depression (22, 23). Thus, being overly sensitive to interpersonal relationship may be considered as a sign of preserved emotional states and affectivity, even if negative and altered. Defining "affectivity" as the capacity to be involved in and to adequately react (both mentally and physically) to the human relationship stimuli (46, 47), we may hypothesised that highly sensitive individuals showed a preserved affectivity, even though pathologically modified. Our results confirmed this relationship at different levels: at a group level, the majority of the sample reported anxiety and mood disorder both at baseline and at follow-up assessment. At a more subjective level, independently from the psychiatric diagnosis, interpersonal awareness and separation anxiety baseline subscales' score were related to the presence of general symptoms, such as depression, irritability, anxiety, sleep disturbances and impaired tolerance to normal stress (as measured by SIPS) at follow-up. The association of interpersonal sensitivity and negative affective states on one hand and attenuated positive psychotic symptoms on the other hand, confirmed the presence of mixed non-psychotic and psychotic psychopathology in adolescents and young adults. As van Os wrote (4): "*The challenge in the years to come is to understand how the earliest expressions of psychopathology form part of a dynamic circuit of symptoms that affect and reinforce each other, gradually differentiating across stages of psychopathology into more specific, but still largely overlapping, clinical syndromes*"; and it has been hypothesised that early psychopathology may evolve in many ways, which do not follow rigid train tracks to full blown mental disorders (1, 7, 16, 17, 49-51).

The lack of long-term follow-up data, the large numbers of drops-out and the young mean age of our sample do not allow us to draw any predictive conclusive value of the role of interpersonal sensitivity on diagnostic outcome. As Lin and colleagues stated (12), continued attenuated positive psychotic symptoms could represent an extended prodrome with transition to psychosis yet to occur or, even if not prodromal, these ongoing distressing and disabling symptoms may be also comorbid with threshold or sub-threshold mood or anxiety disorder. Considering both the high rate of anxiety and mood disorders among our sample and the closely link between interpersonal sensitivity and depressive psychopathological features, we may speculate that our results confirmed this latter hypothesis. On the other hand, highly sensitive individuals who presented with persistent attenuated positive psychotic symptoms may be considered at higher risk to develop longer in time a mood disorders with psychotic feature.

Limitations

The current study presents several major limitations. As already mentioned, the size of our follow-up sample was small (85 individuals in total, instead of the eligible 188) and data about refusal rate were unavailable; a high refusal rate was identified in preliminary baseline data of the same project (33). This significantly limited the statistical power of our analyses. Furthermore, affective symptoms were evaluated by SIPS and not by specific questionnaire for depression other affective symptoms. Finally, the mean follow-up duration was 18 months; recent studies claimed the importance of long-term follow-up since the risk of transition to psychotic disorder extended beyond the first year after presentation, consistent with a lead-time bias (12, 49).

Conclusions

The small sample size of the study does not allow to draw any firm conclusions on ~~whether~~ the role of interpersonal sensitivity on long term diagnostic outcome ~~is relevant and clinically interesting~~. However, assessing level of interpersonal sensitivity when examining young people with subtle, un-specific and transient signs of psychosis, may be considered a useful part of the diagnostic and therapeutic process. Thus, planning targeted

psychotherapeutic interventions focusing on solving self-core fragilities, decreasing interpersonal avoidance and preserving and ameliorating affectivity levels, ~~may~~ could be an important step of early prevention program.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1964 and its later amendments.

References

1. Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK (2014) Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. Schizophrenia Bulletin 40: 120–131.
2. Salokangas RKR, Ruhrmann S, von Reventlow HG, Heinimaa M, Svirskis T, From T, Luutonen S, Juckel G, Linszen D, Dingemans P, Birchwood M, Patterson P, Schultze-Lutter F, Klosterkötter J (2012) EPOS group: Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: prospective follow-up of 245 clinical high-risk outpatients in four countries. Schizophrenia Research 138: 192–197.
3. Svirskis T, Korkeila J, Heinimaa M, Huttunen J, Ilonen T, Ristkari T, McGlashan T, Salokangas RKR (2005) Axis-I disorders and vulnerability to psychosis. Schizophrenia Research 75: 439–446.
4. van Os J (2013) The dynamics of subthreshold psychopathology: implications for diagnosis and treatment. American Journal of Psychiatry 170: 695-698.
5. Yung AR, Nelson B, Thompson A, Wood SJ (2010) The psychosis threshold in Ultra High Risk (prodromal) research: is it valid? Schizophrenia Research 120: 1-6.
6. Fusar-Poli P, Carpenter WT, Woods SW, McGlashan TH (2014) Attenuated Psychosis Syndrome: Ready for DSM-5.1? Annual Review of Clinical Psychology 10: 155–92.
7. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L, Barale F, Caverzasi E, McGuire P (2012) Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Archives of General Psychiatry 69: 220–229.
8. Hartmann JA, Yuen HP, McGorry PD, Yung AR, Lin A, Wood SJ, Lavoie S, Nelson B (2016) Declining transition rates to psychotic disorder in “ultra-high risk” clients: Investigation of a dilution effect. Schizophrenia Research 170: 130-6.
9. Velthorst E, Nieman DH, Becker HE, van de Fliert R, Dingemans PM, Klaassen R, de Haan L, van Amelsvoort T, Linszen DH (2009) Baseline differences in

clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. Schizophrenia Research 109: 60–65.

10. Yung AR, Yuen HP, Berger G, Francey S, Hung TC, Nelson B, Phillips L, McGorry P (2007) Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? Schizophrenia Bulletin 33: 673–681.
11. Addington J, Cornblatt BA, Cadenhead KS, Cannon TD, McGlashan TH, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, Woods SW, Heinssen R (2011) At clinical high risk for psychosis: outcome for nonconverters. American Journal of Psychiatry 168: 800-5.
12. Lin A, Wood SJ, Nelson B, Beavan A, McGorry P, Yung AR (2015) Outcomes of Non-transitioned Cases in a Sample at Ultra-High Risk for Psychosis. American Journal of Psychiatry 172: 249-58.
13. Simon AE, Velthorst E, Nieman DH, Linszen D, Umbricht D, de Haan L (2011) Ultra high-risk state for psychosis and non-transition: a systematic review. Schizophrenia Research 132: 8-17.
14. McGorry P, Nelson B (2016) Why We Need a Transdiagnostic Staging Approach to Emerging Psychopathology, Early Diagnosis, and Treatment. JAMA Psychiatry 73: 191-2
15. Rutigliano G, Valmaggia L, Landi P, Frascarelli M, Cappucciati M, Sear V, Rocchetti M, De Micheli A, Jones C, Palombini E, McGuire P, Fusar-Poli P (2016) Persistence or recurrence of non-psychotic comorbid mental disorders associated with 6-year poor functional outcomes in patients at ultra high risk for psychosis. Journal of Affective Disorders 203: 101-110.
16. McGorry P, Nelson B (2016) Why We Need a Transdiagnostic Staging Approach to Emerging Psychopathology, Early Diagnosis, and Treatment. JAMA Psychiatry 73: 191-2
17. Fusar-Poli P, Bechdolf A, Taylor MJ, Bonoldi I, Carpenter WT, Yung AR, McGuire P (2013) At risk for schizophrenic or affective psychoses? A meta-analysis of DSM/ICD diagnostic outcomes in individuals at high clinical risk. Schizophrenia Bulletin 39: 923-32.
18. van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L (2009) A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. Psychological Medicine 39: 179–195.

19. Ruhrmann S, Schultze-Lutter F, Klosterkotter J (2010) Probably at-risk, but certainly ill—advocating the introduction of a psychosis spectrum disorder in DSM-V. Schizophrenia Research 120: 23–37
20. Woods SW, Miller TJ, McGlashan TH (2001) The “prodromal” patient: both symptomatic and at-risk. CNS Spectrum 6: 223–32.
21. Boyce P, Parker G (1989) Development of a scale to measure interpersonal sensitivity. Australian and New Zealand Journal of Psychiatry 23: 341–351.
22. Boyce P, Mason C (1996) An overview of depression-prone personality traits and the role of interpersonal sensitivity. Australian and New Zealand Journal of Psychiatry 30: 90–103.
23. Boyce P, Parker G, Barnett B, Cooney M, Smith F (1991) Personality as a vulnerability factor to depression. British Journal of Psychiatry 159: 106–114.
24. Häfner H, Riecher-Ro¨ssler A, Hambrecht M, Maurer K, Meissner S, Schmidtke A, Fa¨tkenheuer B, Lo¨ffler W, van der Heiden W (1992) IRAOS: an instrument for the assessment of onset and early course of schizophrenia. Schizophrenia Research 6: 209–223.
25. Hambrecht M, Häfner H, Loffler W (1994) Beginning schizophrenia observed by significant others. Social Psychiatry and Psychiatric Epidemiology 29: 53–60
26. Masillo A, Day F, Laing J, Howes O, Fusar-Poli P, Byrne M, Bhattacharyya S, Fiori Nastro P, Girardi P, McGuire PK, Valmaggia LR (2012) Interpersonal sensitivity in the at-risk mental state for psychosis. Psychological Medicine 42: 1835-1845.
27. Masillo A, Valmaggia LR, Saba R, Brandizzi M, Lindau JF, Solfanelli A, Curto M, Narilli F, Telesforo L, Kotzalidis GD, Di Pietro D, D'Alema M, Girardi P, Fiori Nastro P (2016) Interpersonal sensitivity and functioning impairment in youth at ultra-high risk for psychosis. European Child & Adolescents Psychiatry 25: 7-16.
28. Valmaggia LR, Freeman D, Green C, Garety P, Swapp D, Antley A, Prescott C, Fowler D, Kuipers E, Bebbington P, Slater M, Broome M, McGuire P (2007) Virtual reality and paranoid ideations in people with an ‘at-risk mental state’ for psychosis. British Journal of Psychiatry 51: s63–s68.
29. Valmaggia LR, Day F, Rus-Calafell M (2016) Using virtual reality to investigate psychological processes and mechanisms associated with the onset and maintenance of psychosis: a systematic review. Social Psychiatry and Psychiatric Epidemiology 51:921-36.

30. Davidson M, Reichenberg A, Rabinowitz J, Weiser M, Kaplan Z, Mark M (1999) Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. American Journal of Psychiatry 156: 1328–1335.
31. Freeman D, Garety P (2014) Advances in understanding and treating persecutory delusions: a review. Soc Psychiatry Psychiatr Epidemiol 49: 1179–1189.
32. Green CE, Freeman D, Kuipers E, Bebbington P, Fowler D, Dunn G, Garety P (2011) Paranoid explanations of experience: a novel experimental study. Behavioural and Cognitive Psychotherapy 39: 21–34.
33. Brandizzi M, Schultze-Lutter F, Masillo A, Lanna A, Curto M, Lindau JF, Solfanelli A, Listanti G, Patanè M, Kotzalidis G, Gebhardt E, Meyer N, Di Pietro D, Leccisi D, Girardi P, Fiori Nastro P (2014) Self-reported attenuated psychotic-like experiences in help-seeking adolescents and their association with age, functioning and psychopathology. Schizophrenia Research 160: 110–7.
34. Loewy RL, Bearden CE, Johnson JK, Raine A, Cannon TD (2005) The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. Schizophrenia Research 77: 141–9.
35. Miller TJ, McGlashan TH, Rosen JL, Somjee L, Markovich PJ, Stein K, Woods SW (2002) Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. American Journal of Psychiatry 159: 863–865.
36. Miller TJ, Zipursky RB, Perkins D, Addington J, Woods SW, Hawkins Ka, Hoffman R, Preda A, Epstein I, Addington D, Lindborg S, Marquez E, Tohen M, Breier A, McGlashan TH (2003) The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally. II. Baseline characteristics of the "prodromal" sample. Schizophrenia Research 61: 19-30.
37. Masillo A, Valmaggia LR, Lanna A, Brandizzi M, Lindau JF, Curto M, Solfanelli A, Kotzalidis GD, Patanè M, Godeas L, Leccisi D, Girardi P, Fiori Nastro P (2014) Validation of the Italian version of interpersonal sensitivity measure (IPSM) in adolescents and young adults. Journal of Affective Disorders 156: 164-70.

38. First MB, Spitzer RL, Gibbon M, Williams JBW (1995) Structured Clinical Interview For DSM-IV Axis 1 Disorders Patient Edition (SCID-I/PVersion2.0) NewYork, NY, USA: New York State Psychiatric Institute, Biometrics Research Department.
39. Kaufman J, Bismaher B, Brent DA, Rao U, Flynn C, Moreci P, Williamson D, Ryan N (1997) Schedule for affective disorders and schizophrenia for school-aged children—present and lifetime version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescents Psychiatry 36: 980–988.
40. Kretschmer E (1925) Physique and character: An investigation of the nature of constitution and of the theory of temperament. Harcourt, Brace, Oxford.
41. Sass L, Parnas J (2003) Schizophrenia, consciousness, and the self. Schizophrenia Bulletin 29: 427–444.
42. Nelson B, Parnas J, Sass LA (2014) Disturbance of minimal self (ipseity) in schizophrenia: clarification and current status. Schizophrenia Bulletin 40: 479-482.
43. Nelson, B, Thompson A, Yung AR (2012) Basic Self-Disturbance Predicts Psychosis Onset in the Ultra High Risk for Psychosis “Prodromal” Population. Schizophrenia Bulletin 38: 1277–1287.
44. Nelson B, Sass LA, Skodlar B (2009) The phenomenological model of psychotic vulnerability and its possible implications for psychological interventions in the ultra-high risk (‘prodromal’) population. Psychopathology 42: 283–292
45. Parnas J, Møller P, Kircher T, Thalbitzer J, Jansson L, Handest P, Zahavi D (2005) The Examination of Anomalies of Self-Experience (EASE). Psychopathology 38: 236–258.
46. Fagioli M (1972) Death instinct and knowledge. Excerpts. L’ Asino d’oro, Rome 2010.
47. Maccari S, Polese D, Reynaert ML, Amici T, Morley-Fletcher S, Fagioli F (2017) Early-life experiences and the development of adult diseases with a focus on mental illness: The Human Birth Theory. Neuroscience 7: 232-251.
48. Nelson B, Yuen HP, Wood SJ, Lin A, Spiliotacopoulos D, Bruxner A, Broussard C, Simmons M, Foley DL, Brewer WJ, Francey SM, Amminger GP, Thompson A, McGorry PD, Yung AR (2013) Long-term follow-up of a group at ultra high risk

("prodromal") for psychosis: the PACE 400 study. JAMA Psychiatry 70: 793–802.

49. Nelson B (2014) Attenuated psychosis syndrome: don't jump the gun. Psychopathology 47: 292-6.

50. Yung AR, Nelson B, Baker K, Buckby JA, Baksheev G, Cosgrave EM (2009) Psychotic-like experiences in a community sample of adolescents: implication for the continuum model of psychosis and prediction of schizophrenia. Australian and New Zealand Journal of Psychiatry 43: 118-128

51. Woods SW, Addington J, Cadenhead KS, Cannon TD, Cornblatt BA, Heinssen R, Perkins DO, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH (2009) Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. Schizophrenia Bulletin 35: 894–908.

Table 1: Socio-demographic and clinical characteristics of the sample at baseline and correlation with IPSM subscales (N=85)

	Mean	*SD*	IPSM correlation (Mann-Whitney; Kruskal-Wallis)
Age	16.36	5.05	
	n	%	
Gender			Total**;interpersonal**; separation**; timidity*
- Female	40	47.10	
- Male	45	52.90	
Educational level			
- Primary school	28	32.90	
- Junior high school	43	50.60	
- Senior high school	12	14.10	
-Professional school	2	2.40	
- University	0	0	
Employment status			
- Student	28	32.90	
- Unemployed	43	50.60	
- Employee	12	14.10	
- Temporary employee	2	2.40	
	0	0	
Reason for referral			
- Anxiety	23	27.05	
- depression/mood liability	19	22.35	
-psychotic symptoms	2	2.40	
- agitation/violence	6	7.10	
- suicide ideas or attempting	2	2.40	
- eating disorders	1	1.20	
- school problems	20	23.50	
- relational problems	11	12.90	
- obsessive symptoms	1	1.20	
Psychiatric diagnosis			
- No diagnosis	4	4.70	
-Anxiety disorder	29	34.10	
-mood disorder	27	31.80	
-personality disorder	6	7.10	
- adjustment disorder	9	10.60	
- childhood disorder (conduct-learning)	8	9.40	
Previous psychiatric treatment			
-No	43	50.60	
-Psychotherapy	29	34.10	
-Pharmacological	7	8.20	
-Combined	4	4.70	
- Psycho-education	2	2.40	
SIPS category			
-N-UHR	55	65.50	
-APS	28	33.30	
-BLIPS	0	0	
-GRDS	1	1.20	
	Mean	*SD*	
IPSM			
- Interpersonal awareness	19.42	4.78	
-Need for approval	23.41	4.54	
- Separation anxiety	21.13	5.52	
- Timidity	20.08	5.04	
-Fragile inner-self	10.64	4.17	
-Total	94.55	18.05	

SIPS			
-Positive	4.80	4.24	Fragile**
-Negative	7.83	6.03	
-Disorganised	3.90	3.37	Fragile**;
-General	5.20	3.49	Interpersonal*; separation**; fragile*

*:p≤0.05;**:p≤0.005;
N-UHR: subjects non-UHR according to SIPS; total: IPSM total; need: IPSM need for approval; separation: IPSM separation anxiety; interpersonal: IPSM interpersonal awareness; fragile: IPSM fragile inner self; timidity: IPSM timidity.

Table 2: Socio-demographic and clinical characteristics of the sample at 18-months follow-up and correlation with IPSM subscales (N=85)

	Mean	*SD*	IPSM correlation (Mann-Whitney; Kruskal-Wallis)
Time between T0 and T1	17.65	8.81	
Age	18.25	5.28	
	n	%	
Psychiatric treatment between T0 and T1			
-No	36	42.90	
- Yes	48	57.10	
Psychiatric diagnosis			
- No diagnosis	1	1.20	
-Anxiety disorder	29	34.10	
-Mood disorder	32	37.60	
-Personality disorder	18	21.20	
- Adjustment disorder	1	1.20	
-First Episode Psychosis	4	4.60	
SIPS category			
-N-UHR	56	65.90	
-APS	23	27.10	
-BLIPS	2	2.40	
-GRDS	0	0	
-Transition to psychosis	4	4.70	
	Mean	*SD*	
SIPS			
-Positive	5.19	5.33	Fragile*
-Negative	9.38	8.12	
-Disorganised	4.04	3.50	
-General	4.85	4.01	Interpersonal**; separation*

*:p≤0.05;**:p≤0.005;
N-UHR: subjects non-UHR according to SIPS; total: IPSM total; need: IPSM need for approval; separation: IPSM separation anxiety; interpersonal: IPSM interpersonal awareness; fragile: IPSM fragile inner self; timidity: IPSM timidity.

Model					t	Sig.	95% CI		ANOVA	
		B	SE	Beta			L	B	F	p
I	(Constant)	6.625	3.245		2.041	.045	.165	13.084	2.753	0.024
	IPSM: interpersonal awareness	.244	.162	.218	1.506	.136	-.078	.566		
	IPSM: need for approval	-.268	.152	-.228	-1.767	.081	-.570	.034		
	IPSM: separation anxiety	-.004	.146	-.004	-.024	.981	-.295	.288		
	IPSM: timidity	-.151	.129	-.142	-1.166	.247	-.408	.106		
	IPSM: fragile inner self	.301	.161	.235	1.873	.065	.019	.621		
II	(Constant)	6.881	3.039		2.264	.026	.835	12.341	5.328	0.007
	IPSM: need for approval	-.250	.124	-.214	-2.019	.047	-.497	.004		
	IPSM: fragile inner self	.392	.135	.306	2.898	.005	.123	.661		

Table 3: Model summary predicting positive SIPS symptoms at follow-up. Final model R^2=0.115; adjusted R^2=0.093

Model					t	Sig.	95.0% CI		ANOVA	
		B	SE	Beta			L	U	F	p
I	(Constant)	3.813	2.365		1.613	0.111	-.474	7.989	4.021	0.003
	IPSM: interpersonal awareness	0.331	0.118	0.394	2.806	0.006	.077	.501		
	IPSM: need for approval	-0.316	0.110	-0.357	-2.856	0.005	-.452	-.052		
	IPSM: separation anxiety	0.188	0.107	0.259	1.765	0.081	-.027	.355		
	IPSM: timidity	-0.007	0.094	-0.008	-0.072	0.943	-.206	.132		
	IPSM: fragile inner self	-0.173	0.117	-0.180	-1.480	0.143	-.354	.066		
II	(Constant)	3.52	2.294		1.534	0.129	-.761	7.440	7.956	0.001
	IPSM: interpersonal awareness	0.362	0.093	0.431	3.873	0.000	.138	.475		
	IPSM: need for approval	-0.243	0.098	-0.276	-2.480	0,015	-.374	-.021		

Table 4: Model summary predicting general SIPS symptoms at follow-up. Final model R^2=0.163; adjusted R^2= 0.142